02-01-07

Attorney's Docket No.: 19049-005001/4905

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nguyen et al.	Art Unit	: 1639
Serial No.	: 10/677,977	Examiner	: Teresa D. Wessendorf
Filed	: October 2, 2003	Conf. No.	: 9061
Cust. No	: 20985		
Title	: METHODS OF GENERATING AND SCREENING FOR PROTEASES WITH ALTERED SPECIFICITY		

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a Petition Under 37 C.F.R. §1.144 Petition From Requirement For Restriction response to the to the Office Action, mailed November 30, 2006, (16 pages); and a check $130.00 for the requisite fee for a petition and a return postcard. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Fee for a Petition to the Director:

☒ By a small entity.....$130.00

☒ The Commissioner is hereby authorized to charge the fee for the extension of time and any other fee that may be due in connection with this and the attached papers or with this application during its entire pendency to Deposit Account No. 06-1050. A duplicate of this sheet is enclosed.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 19049-005001/4905

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I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

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Title : METHODS OF GENERATING AND SCREENING FOR PROTEASES WITH ALTERED SPECIFICITY FOR SELECTED TARGETS

PETITION UNDER 37 C.F.R. §1.144
PETITION FROM REQUIREMENT FOR RESTRICTION

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby petitions under 37 C.F.R. §1.144 from a Restriction Requirement in the above-captioned application. Applicant requests removal of the Requirement as between and among Group I (claims 1-7, 9, 11-16, 45-48 and 50-52), Group II (claims 53, 54 and 56-58), Group III (claims 59-62) and Group IV (claims 63-66). It respectfully is submitted that Applicant timely traversed the Requirement for Restriction and provided arguments thereto, contrary to the assertion by the Examiner in the Non-Final Office Action mailed November 30, 2006, in which the requirement for restriction was made final. Applicant is providing this petition in accordance with the rules set forth in 37 C.F.R. §1.144 since reconsideration of the requirement was requested.

Accordingly, Applicant respectfully requests rejoinder of Group I, Group II, Group III and Group IV for examination in this application. It respectfully is submitted that each of Groups I-IV is related insofar as the claimed subject matter is overlapping. Hence, the subject matter of each of Groups I-IV is not mutually exclusive. Notwithstanding this, it also is respectfully submitted that the requirement is improper insofar as claims in Group I are related to claims in Group III as a genus/species and claims in Group III are related to claims in Group IV as a genus/species. In fact, in one instance, identical claims, inadvertently included in the application, are restricted into different Groups, evidencing errors in the requirement.

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I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Stephanie Seidman

It further is noted that statements made by the Examiner in the Non-Final Office Action mailed November 30, 2006 are not accurate. For example, the Examiner notes that Applicant elected *Group III*, claims 63-66, when in fact Applicant elected **Group IV** directed to claims 63-66. In addition, the Examiner notes that claims 1-7, 9, 11-16, 45-48, 50-54 and 56-**63** are withdrawn. Claim 63 is not withdrawn; it is among the claims in elected Group IV.

STATEMENT OF FACTS

The Requirement for Restriction, provided as a written Restriction Requirement, mailed April 11, 2006, sets forth four (4) Groups for election. Applicant elected, with traverse, Group IV, claims 63-66, and requested reconsideration of the Requirement as between and among Groups I-IV in the Election and Preliminary Amendment, mailed September 11, 2006. In an Office Action, mailed November 30, 2006, the Election was deemed to be an election without traverse. The undersigned, on behalf of Applicant, telephoned the Examiner requesting reconsideration of the Requirement for Restriction based on the clear traversal of the Requirement as set forth in the Election and Preliminary Amendment, mailed September 11, 2006. The Requirement for Restriction was maintained by the Examiner.

ARGUMENT

Applicant respectfully petitions for reconsideration and removal of the Requirement as between and among Group I (claims 1-7, 9, 11-16, 45-48 and 50-52), Group II (claims 53, 54 and 56-58), Group III (claims 59-62) and Group IV (claims 63-66) in view of the following remarks and those of record. Alternatively, Applicant petitions as between Group I and Group III and as between Groups III and Group IV in view of the following remarks.

Restrictions as between and among Groups I, II, III and IV

The Office Action, mailed April 11, 2006, urges that the Restriction Requirement is based on the premise that the various Groups are patentably distinct because they are unrelated due to different modes of operation, different functions or different effects. It is alleged that the methods are unrelated because they are drawn to different methods comprising different components and/or method steps. Applicant respectfully submits that restriction between Groups I-IV is improper for the reasons set forth in detail below.

It respectfully is submitted that each of Groups I, II, III and IV is related to each of the others because they encompass overlapping subject matter. Inventions that are related are distinct and restriction may be proper ***only if*** it can be shown that (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode

of operation, function or effect; (2) the inventions do not overlap in scope, i.e. are mutually exclusive; **and** (3) the inventions as claimed are not obvious variants. See MPEP 806.05(j). Applicant respectfully submits that in this instance Groups I, II, III and IV contain overlapping subject matter.

Each of Groups I (claims 1-7, 11-16, 45-48 and 50-52); Group II (claims 53, 54, and 56-58); Group III (claims 59-62); and Group IV (claims 63-66) is directed to a method of identifying a protease mutein that cleaves a substrate sequence in a target protein involved in a pathology. The presence of overlapping subject matter between the four groups is evident if one compares the steps of the methods and the components of the method as recited in claims of each of the groups. For example, the Table below separates each element and/or step of the methods as recited in independent claim 1 (Group I), independent claim 53 (Group II), independent claim 59 (Group III) and independent Claim 63 (Group IV) to illustrate the overlapping subject matter among these Groups. Dependent claims also are including in the Table in italics to further illustrate the overlapping subject matter between and among the Groups. The elected species of granzyme B and caspases-3 are denoted in bold to emphasize the overlapping subject matter among the restricted Groups. To more clearly illustrate the overlapping subject matter, common steps of the methods and/or elements of the method are grouped together in the Table below. The wherein clauses in the claims are not necessarily listed in the order in which they appear in the claim (an inadvertent duplication of a wherein clause in claim 59 is included below). The subject matter, however, of the claims is accurately set forth.

TABLE

Group I	Group II	Group III	Group IV
Claim 1: A method of identifying a mammalian protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:	**Claim 53:** A method of identifying a mammalian protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:	**Claim 59:** A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a human, wherein:	**Claim 63:** A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:
cleavage of said substrate sequence in said target protein serves as a treatment for said pathology; and	cleavage of said sequence in said target protein serves as a treatment for said pathology;	cleavage of said sequence in said target protein serves as a treatment for said pathology;	cleavage of said sequence in said target protein serves as a treatment for said pathology; and
the method comprising the steps of: (a) producing a library of protease muteins, each different	the method comprising the steps of: (a) producing a library of protease muteins, each different protease mutein	the method comprising the steps of: (a) producing a library of protease muteins, each different protease mutein	the method comprising the steps of: (a) producing a library of human protease muteins, each different

Group I	Group II	Group III	Group IV
mutein protease in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold wherein N is a positive integer;	in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold, wherein N is a positive integer;	in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold, wherein N is a positive integer,	protease mutein in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of a human protease wherein N is a positive integer,
Claim 7: *The method of claim 1, wherein the mammalian protease scaffold has an amino acid sequence derived from one of the proteases selected from among trypsin, chymotrypsin, subtilisin, MTSP-1, granzyme A, **granzyme B**, and granzyme M, elastase, chymase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin and cruzain.*	the mammalian protease is selected from among granzyme A, **granzyme B**, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin, and cruzain;) and	wherein said protease is selected from among granzyme A, **granzyme B**, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin and cruzain;	wherein said human protease is selected from among granzyme A, **granzyme B**, granzyme M, cathepsin, MTSP-1, elastase, chymase, tryptase, chymotrypsin, collagenase, factor Xa, Protein C, plasma kallikrein, plasmin, trypsin, thrombin, complement factor serine proteases, papain, ADAMTS13, endopeptidase, furin, cruzain and plasminogen activator;
(b) measuring an activity of at least two members of the library in cleaving the substrate sequence; and	(b) measuring an activity of at least two members of the library in cleaving the substrate sequence;	(b) measuring an activity of at least two members of the library in cleaving the substrate sequence,	(b) measuring an activity of at least two members of the library in cleaving the substrate sequence,
the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; ***Claim 11:*** *The method of claim 1, wherein the target protein is involved in apoptosis.* ***Claim 12:*** *The method of claim 11, wherein the target protein is **caspase-3**, VEGF or VEGF-R.*		wherein the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and ***Claim 62.*** *The method of claim 59, wherein the target protein is selected from among **caspase 3**, tumor necrosis factor, tumor necrosis factor*	wherein said target protein is selected from among **caspase 3**, tumor necrosis factor, tumor necrosis factor receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand, Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, hemagglutinin, respiratory syncytium

Group I	Group II	Group III	Group IV
		receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand, Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, hemagglutinin, respiratory syncytium virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2) and cyclin dependent kinase-4 (cdk-4).	virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2), and cyclin dependent kinase-4 (cdk-4); and
(c) identifying at least one mutein protease having an increased cleavage activity and/or altered specificity for cleaving said substrate sequence, relative to the wild-type mammalian scaffold.	(c) identifying at least one protease mutein having a measured increase in cleavage activity and/or altered specificity for cleaving said substrate sequence relative to the wild-type mammalian protease scaffold;	(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold.	(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold.
Claim 16. *The method of claim 1, further comprising the steps of: (d) providing two or more members of the protease library identified with increased cleavage activity and/or altered specificity;*	(d) providing two or more members of the protease mutein library identified with increased cleavage activity and/or altered specificity for cleaving said substrate sequence;		

Group I	Group II	Group III	Group IV
(e) combining the mutations on a first mutein protease with the mutations on a second mutein protease to produce a third mutein protease; and	(e) combining mutations in a first mutein with increased cleavage activity with mutations in a second mutein to produce a third mutein; and		
(f) identifying whether the combination produces a combined specificity protease that has increased cleavage activity and/or altered specificity for the substrate sequence.	(f) identifying whether the third mutein produces a protease that has increased cleavage activity toward the substrate sequence and/or altered specificity for cleaving said substrate sequence.		

A summary of the subject matter of each of Groups I, II, III and IV is described below with reference to the recited claims set forth in the Table above.

Group I

Independent claim 1 (and dependent claims 2-7, 11-16, 45-48, and 50-52) is directed to a method of identifying a modified mammalian protease that cleaves a substrate sequence in a target protein by recited steps. The target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor, and a signaling protein that regulates apoptosis. The protease is not specified. Dependent claim 7 recites a list of proteases, including granzyme B, and dependent claim 12 specifies that the target protein is selected from among caspases-3, VEGF and VEGFR. Further, dependent claim 16 sets forth additional steps of the methods (d)-(f).

Group II

Independent claim 53 (and its dependents 54, and 56-58) also is directed to a method of identifying a modified mammalian protease that cleaves a substrate sequence in a target protein by recited steps. The mammalian protease is set forth among a group of listed proteases, including granzyme B. The recited methods steps are the recited method steps (a)-(f) set forth in Group I above.

Group III

Independent claim 59 (and its dependents 60-62) is directed to a method of identifying a modified human protease that cleaves a substrate sequence in a target protein by recited steps, where the target protein is selected from among the same target proteins set forth in Group I. The claim specifies that the target protein is involved with a pathology in a

human. The recited method steps are the same recited method steps (a)- (c) in Group I, except that step (a) specifies that the protease is selected from among a list of proteases, including granzyme B. Dependent claim 62 specifies that the target protein is selected from a list of proteins, including caspase 3.

Group IV

Independent claim 63 (and its dependents 64-66) is directed to a method of identifying a modified human protease that cleaves a substrate sequence in a target protein by recited steps. The recited steps are the same as steps (a)- (c) in Group I, except step (a) sets forth a list of proteases, including granzyme B; and step (b) sets forth a list of target proteins, including caspases 3.

Hence, each of Groups I-IV is directed to a method of identifying a modified protease involving the same or similar recited steps. For example, Group I sets forth steps (a) – (c), which are the same steps as recited in each of Groups III and IV. Dependent claim 16 of Group I sets forth additional steps (d) – (f) thereby providing for steps (a) – (f), which are the same as the steps of the method set forth in claim 53 of Group II. Although the list of protease or target proteins used in the methods of each of the Groups are different, they are overlapping in subject matter. For example, each of Groups I-IV specify that the protease can be granzyme B. Also, each of Groups I, III and IV specify that the target protein can be caspase 3. The subject matter of Group II also encompasses a target protein that is caspase 3 because the target protein is not specified.

The presence of overlapping subject matter among the claims of Groups I, III and IV is apparent since all of the groups read on the elected species of a method involving a granzyme B protease and a caspase 3 target protein. Each of claims 1, 59, and 63 of Groups I-IV, respectively, encompass subject matter of the elected species. Group II is encompassed with in Group I. Hence, claims in Groups I-IV are related, insofar as they contain overlapping subject matter.

Accordingly, the methods of non-elected Groups read on the elected species of the method of Group IV. For example, the elected species of the method of claim 63 of Group IV recites:

> A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:
>
> cleavage of said sequence in said target protein serves as a treatment for said pathology; and

the method comprising the steps of:

(a) producing a library of human protease muteins, each different protease mutein in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of a human protease wherein N is a positive integer, wherein said human protease is **granzyme B**;

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein said target protein is **caspase 3**; and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold

For example, the method of claim 1 in Group I encompasses the subject matter of the elected species of the method because the method includes the same steps as set forth in the method of the elected species, where the protease used in the method can be any protease and the target protein selected for cleavage can be a signaling protein that regulates apoptosis. Dependent claims 7 and 12 of Group I further encompass the subject matter of the elected species of the method because they specify that the protease can be granzyme B (claim 7) and that the target protein can be caspase 3 (claim 12). Claims in Group III also encompass the elected species of the method of claim 63 in Group IV. Claim 59 of Group III includes the same method steps of claim 63 in Group IV, where the target protein selected for cleavage can be a signaling protein that regulates apoptosis and the protease can be granzyme B. Dependent claim 62 further encompasses the subject matter of the elected species of the method because it specifies that the target protein selected for cleavage in the method can be caspase 3. As noted above, Group I encompasses Group II.

Thus, the methods of Groups I-IV are not mutually exclusive. Therefore, as between Group I, II, III and IV, restriction is not proper. Since such restriction is improper, reconsideration and withdrawal of the restriction requirement as between Groups I-IV respectfully are requested.

Multiple Patents

If the claims are restricted into these four groups, Applicant ultimately could be granted four patents containing overlapping subject matter, each of which could expire on different dates and could be owned by a different assignee. The claims of any later issuing patent of any of Groups I, II, III or IV could not be held to constitute obvious-type double patenting over an earlier issuing patent claiming overlapping subject matter. As shown above, claims in Groups I, III and IV read on the elected species of the method. Claims in Group II also overlap in subject matter with claims in Group I. If a patent to elected Group

IV, which includes the elected species of the method issues before patents with claims to any of Groups I and III, the Office, however, will be precluded from rejecting any of these claims based on obviousness-type double patenting over a claim to the elected species. Similarly, if claims in Group II issue before claims in Group I, a finding of obviousness-type double patenting will be precluded. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office [obviousness-type] double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP §804.01, which states:

> 35 U.S.C. §121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. §121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Hence, if the restriction requirement as between Groups I-IV is maintained, the Office is precluded from rejecting any of the claims in any of Groups I and III over any of the claims or subject matter of Group IV, and claims of Group I over claims of Group II. Therefore, the requirement for restriction among Groups I-IV is incorrect. Reconsideration of the requirement for restriction among Groups I-IV respectfully is requested.

Restriction as between Groups I and III and Group III and IV

It respectfully is submitted that in addition to overlapping subject matter among Groups I-IV, Group I is related to Group III as a genus/species; and Group III is related to Group IV as a genus/species. Accordingly, if the above arguments regarding overlapping subject matter among all groups is not persuasive, Applicant respectfully requests reconsideration of the requirement for restriction as between Group I and Groups III and as between Group III and Group IV.

Group I and III

Claim 1 of Group I is directed to a method of identifying a *mammalian* protease that cleaves a substrate sequence in a target protein. The target protein is identified as one that belongs to any of a class of proteins such as a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor, and a signaling protein that regulates apoptosis. The protease used in the method is not specified. The steps in the methods include specific recited steps.

Independent claim 1 recites:

A method of identifying a mammalian protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:

the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis;

cleavage of said substrate sequence in said target protein serves as a treatment for said pathology; and

the method comprising the steps of:

(a) producing a library of protease muteins, each different mutein protease in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold wherein N is a positive integer;

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence; and

(c) identifying at least one mutein protease having an increased cleavage activity and/or altered specificity for cleaving said substrate sequence, relative to the wild-type mammalian scaffold.

Claim 59 of Group III is directed to a method of identifying a *human* protease. The steps in the method and the recitation of the target protein are the same as claim 1 of Group I. The protease used in the method, however, is selected from a list of proteases.

Independent claim 59 of Group III recites:

A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a human, wherein:

cleavage of said sequence in said target protein serves as a treatment for said pathology;

the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and

the method comprising the steps of:

(a) producing a library of protease muteins, each different protease mutein in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold, wherein N is a positive integer, wherein said protease is selected from among granzyme A,

granzyme B, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin-and cruzain;

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold.

Thus, claim 1 of Group I is directed to a genus of a method of a identifying a mammalian protease encompassing a genus of target proteins and a genus of proteases. Claim 59 of Group III is directed to a species of the method where the mammalian proteases are human and the proteases are specified. Thus, claim 1 and claim 59 are related as genus/species. Genus claims linking species claims are one example of linking claims. See MPEP §809.03. Thus, claim 1 is a linking claim and must be examined with Group III. Pursuant to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on:

1) specifying the linking claims; and

2) examining the linking claims with the elected group. The linking claims must be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined. Therefore, Groups I and III are linked.

Also, it is apparent that this requirement is improper if one considers the outcome if patents issued based upon each of these two groups. If the claims are restricted into these two groups, Applicant ultimately could be granted two patents that expire on different days and/or are not required to be commonly owned. For example, if claim 59 in Group III issues before claim 1 in Group I, the issued patent will include a claim (*i.e.* claim 59) that is a species of claim 1. Claim 1, which could be pending in another divisional application, encompasses the species in claim 59. The Office, however, will be precluded from rejecting it based on obviousness-type double patenting over claim 59. The Examiner is reminded of the cautionary language in MPEP §806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP §804.01, which states:

> 35 U.S.C. §121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. §121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

In this instance, if the restriction requirement as between Groups I and III is maintained, the Office is precluded from rejecting the claims for obviousness-type double patenting. Therefore, reconsideration of the requirement for restriction as between these groups is respectfully requested.

Group III and IV

Claim 62 of Group III, dependent from and including all of the limitations of independent claim 59, is directed to a method of identifying a human protease that cleaves a substrate sequence in a target protein. The target proteins and proteases used in the method are selected from a list of proteins. The steps in the methods include specific recited steps.

Independent claim 59 recites:

> A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a human, wherein:
>
> cleavage of said sequence in said target protein serves as a treatment for said pathology;
>
> the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and
>
> the method comprising the steps of:

(a) producing a library of protease muteins, each different protease mutein in the library being a member of the library, each member having N mutations relative to a wild-type mammalian protease scaffold, wherein N is a positive integer, wherein said protease is selected from among granzyme A, granzyme B, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin-and cruzain;

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein the target protein is selected from among a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor and a signaling protein that regulates apoptosis; and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold.

Dependent claim 62 recites:

The method of claim 59, wherein the target protein is selected from among caspase 3, tumor necrosis factor, tumor necrosis factor receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand, Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, hemagglutinin, respiratory syncytium virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2) and cyclin dependent kinase-4 (cdk-4).

Claims 65 and 66 of Group IV, dependent from and including all of the limitations of independent claim 63 of Group IV, further specify the protease or the target protein, respectively, from among a smaller list of proteins. As discussed in detail below, it also is noted that claim 62 of Group III is virtually identical to claim 63 of Group IV; this inadvertent error will be addressed in the next response.

Independent claim 63 of Group IV recites:

A method of identifying a human protease mutein that cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein:

cleavage of said sequence in said target protein serves as a treatment for said pathology; and

the method comprising the steps of:

(a) producing a library of human protease muteins, each different protease mutein in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of a human

protease wherein N is a positive integer, wherein said human protease is selected from among granzyme A, granzyme B, granzyme M, cathepsin, MTSP-1, elastase, chymase, tryptase, chymotrypsin, collagenase, factor Xa, Protein C, plasma kallikrein, plasmin, trypsin, thrombin, complement factor serine proteases, papain, ADAMTS13, endopeptidase, furin, cruzain and plasminogen activator;

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein said target protein is selected from among caspase 3, tumor necrosis factor, tumor necrosis factor receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand, Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, hemagglutinin, respiratory syncytium virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2), and cyclin dependent kinase-4 (cdk-4); and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type mammalian protease scaffold.

Dependent claim 65 recites:

The method of claim 63, wherein the protease is selected from among granzyme A, granzyme B, granzyme M and MTSP-1.

Dependent claim 66 recites:

The method of any one of claims 63-65, wherein the target protein is selected from among caspase 3, vascular endothelial growth factor and VEGF receptor.

Thus, claim 62 is directed to a method encompassing a genus of proteases and a genus of target proteins, and claims 65 and 66 are each directed to a species of the method where the proteases (claim 65) and target proteins (claim 66) are specified. Thus, claim 62 of Group III and claims 65 and 66 of Group IV are related as genus/species. Genus claims linking species claims are one example of linking claims. See MPEP §809.03. Thus, claim 62 is a linking claim and must be examined with Group IV. Pursuant to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on:

1) specifying the linking claims; and

2) examining the linking claims with the elected group. The linking claims must be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject

matter that depends from or includes all the limitations of the linking claims must be rejoined. Therefore, Groups III and IV are linked.

Also, it is apparent that this requirement is improper if one considers the outcome if patents issued based upon each of these two groups. If the claims are restricted into these two groups, Applicant ultimately could be granted two patents that expire on different days and/or are not required to be commonly owned. For example, if claim 65 and/or claim 66 in Group IV issues before claim 62 in Group III, the issued patent will include a claim (*i.e.* claim 65 or 66) that is a species of claim 62. Claim 62, which could be pending in another divisional application, encompasses the species in claims 65 or 66. The Office, however, will be precluded from rejecting them based on obviousness-type double patenting over claim 62. The Examiner is reminded of the cautionary language in MPEP §806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP §804.01, which states:

> 35 U.S.C. §121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. §121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

In this instance, if the restriction requirement as between Groups III and IV is maintained, the Office is precluded from rejecting the claims for obviousness-type double patenting. Therefore, reconsideration of the requirement for restriction as between these groups is respectfully requested.

Identical Subject Matter

Notwithstanding the above arguments, it also is apparent that the requirement for restriction is improper since claimed subject matter in Group III and Group IV is identical. In this instance, claim 62 of Group III, incorporating the limitations of independent claim 59, is identical to independent claim 63 of Group III. Hence, restriction as between Groups III and IV is not proper because the claims in Group III (i.e. claim 62) are not distinct from claims in Group IV (i.e. claim 63). The presence of the identical subject matter in different claims was inadvertent; Applicant will correct this in the next response.

* * *

In view of the above, Applicant hereby petitions for reconsideration and removal of the Restriction Requirement as between and among Group I (claims 1-7, 9, 11-16, 45-48 and 50-52), Group II (claims 53, 54 and 56-58), Group III (claims 59-62) and Group IV (claims 63-66); as between Group I and Group III; and as between Group III and IV. Since Applicant has elected Group IV, with traverse, in the instant application, it respectfully is requested that claims in each of Group I, Group II, Group III and Group IV, be combined for examination herein.

Enclosed herewith is a check including the fee for this Petition. If the accompanying fee is incorrect or missing or should additional fees be required, authorization is hereby given to charge Deposit Account No. 06-1050.

Respectfully submitted,

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